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A Second Season's Experience of Hyper- tonic Transfusions in Cholera Controlled by Observations on the Blood Changes

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A SECOND SEASON'S EXPERIENCE OF HYPERTONIC TRANSFUSIONS IN CHOLERA CONTROLLED BY OBSER- VATIONS ON THE BLOOD CHANGES.

BY LEONARD ROGERS, M.D., F.R.C.P.,
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The great majority of cholera patients are admitted in the collapse stage of the disease or very soon pass into it. This is obviously mainly due to the great loss of fluid from the body by the copious vomiting and watery stools, the latter often amounting to several pints at a time. As, however, Dr. George Johnson, in his advocacy of the evacuant treatment of cholera, as late as 1866, denied that there is any relationship between the loss of fluid and the death-rate of the disease, I have investigated the blood changes from this point of view. The results were published in the *Proceedings of the Royal Society* early this year, so need only be summarized here. In a severe case of cholera the great concentration of the blood is at once apparent on opening a vein, while a blood count shows seven to eight million red corpuscles per cubic millimeter. The specific gravity is raised from 1056 to 1065 to 1075. In order to obtain a more accurate measure of the loss of

fluid from the blood I have rapidly defibrinated it or mixed it with a known quantity of citrate of soda solution, and centrifuged in the hemocrit, the respective volumes of corpuscles and serum being thus at once obtained. The normal volume of corpuscles in the natives of India, on whom nearly all my observations have been made, is 45 per cent, but in cholera collapse they usually form from 60 to 70 per cent, or rarely 80 per cent. As the red corpuscles are not lost to the system the amount of reduction of the serum can be calculated from these data, and the relationship of the degree of loss to the death-rate ascertained. The results of this investigation showed that in the most severe type, proving fatal in spite of transfusion, the average loss of serum amounted to 64 per cent of the total; in severe cases requiring transfusion, but with ultimate recovery, it averaged 52 per cent; while in the mild type, in which transfusion was not necessary, the loss was only 35 per cent of the whole. There is thus a very definite relationship between the loss of fluid from the blood and the severity of the disease, which in cases that are at all severe is so great as to clearly indicate a line of treatment directed toward its replacement in order to lessen the concentration of the blood and to restore the failing circulation.

THE BLOOD-PRESSURE AS A GUIDE TO TRANSFUSION IN CHOLERA.

A yet more valuable guide in the treatment of the collapse stage is the blood-pressure, which has the additional advantage of being more readily available. The normal figure for natives of India is somewhat lower than for Europeans, namely, from 100 to 110 mm. As a result of two years' experience I look upon a pressure of not over 70 in men, or a little lower in women, as an indication for intravenous injections of saline solutions as opposed to less rapid methods of replacing the lost fluid. The presence of marked restlessness or cramps is also an indication for this measure, especially if accompanied by cyanosis in the collapse stage. Moreover, the blood-pressure is a most valuable guide to the amount of fluid to be injected, a rise to over 100 mm. being aimed at, although in some cases with marked vasomotor paralysis it is not possible to reach this point. The importance of watching the blood-pressure during transfusion is that the finger is often a very fallacious guide in these cases. After one or two pints the pulse may appear to be quite a good one, whereas the manometer shows the pressure to be not over 80 mm., and if the injection is stopped at this point a rapid relapse is exceedingly probable. From a perusal of the writings of

Wall and others I feel sure that one reason why the benefit derived from this measure was very evanescent was that too little fluid had been given to restore the normal blood-pressure. This view is borne out by a number of observations I have made on the volumes of blood-corpuscles and serum before and after transfusions with given quantities of salt solutions. These have shown that in severe collapse not less than four pints in adult males, and somewhat less in females, are required to dilute the blood down to or, better, a little below the normal, to allow for some subsequent loss, while I have met with cases in which even this amount left the blood more concentrated than normal. The specific gravity of the blood is a useful control as to the degree of dilution obtained, reduction to a point several degrees below the normal being advisable and safe.

METHODS OF REPLACING THE LOSS OF FLUIDS IN CHOLERA.

There are a variety of ways of introducing fluid into the system, the choice of one or more of which will depend on the severity of the case. Water or normal saline may always be freely given by the mouth, and although it is frequently vomited some toxin is probably evacuated with it.

Rectal Injections.—Of much greater practical importance is the use of saline

enemata, for the large bowel has not lost its power of absorption, and will frequently retain a pint of fluid long enough for most of it to enter the system. When there is a fair pulse, a pint of saline by the rectum every two hours will often suffice to tide the patient over the danger of collapse. If, however, the blood-pressure is very low this fluid is not absorbed quickly enough to save the patient, and more vigorous measures are necessary. In border-land cases with a still clearly perceptible pulse, but a blood-pressure nearly at the point at which I advise intravenous injections, namely 70 mm., I have recently used continuous rectal injections at the rate of one ounce a minute (three pints an hour), with the desired result of raising the pressure and avoiding the necessity for the much more troublesome intravenous administration. Where the patient can be closely watched, everything being kept in readiness for injection if further collapse ensues, this simple measure promises to be of considerable value. The rate of flow can be readily regulated by means of a wooden stop-cock in the tubing, the glass bulb containing the saline being marked with a diamond to show every two ounces of its capacity. The time it takes for two ounces to run in is noted, and the tap regulated until the required rate is attained.

Subcutaneous Injection.—The injection of from half to one pint of saline into the subcutaneous tissues of the chest, axilla, or thighs, has been largely used in India in the treatment of cholera. If there is a fair pulse the fluid is readily absorbed and will certainly save some cases, so subcutaneous injections may be recommended when the much more efficient intravenous method is not practicable. The great drawbacks are the difficulty of rapidly getting in sufficient fluid, and the frequency with which the extensive abscesses result, in spite of the utmost care, on account of the low vitality of the tissues in cholera. For these reasons I never use it in hospital practice where the intravenous injections are feasible. When subcutaneous injections have to be used the slow continued method of administration is most likely to be successful.

Intra-abdominal Injections.—An easier and more rapid way of introducing large quantities of salines into the system is by intraperitoneal injections by means of a cannula I have devised for the purpose. When the circumstances or number of cases prevent the use of intravenous injections it promises to be a valuable substitute.

Intravenous Injections; The Comparative Failure of Normal Saline Solutions.—In all really severe cases of cholera collapse, with little or no pulse at the wrist, the intrave-

nous injections can alone be relied on to snatch the patient from a rapid death. Hitherto normal saline solution, one drachm of sodium chloride to a pint of water, or 0.65 per cent solution, has almost invariably been used for this purpose. The marvelous immediate effect in reviving the patient is universally acknowledged, but unfortunately it is equally well known, ever since the method was first introduced by Drs. Latta and Mackintosh of Edinburgh in the English epidemic of 1831-32, that in a considerable majority of cases the benefit is only temporary, and even repeated injections usually fail to save the patients. The introducers of the method had a mortality of 84 per cent in 166 cases, while Wall, who in his book published in 1893 enthusiastically advocates the repeated use of the measure, had a mortality of a little over 70 per cent in 193 cases, in spite of the advantages of the aseptic system. Goodeve states that the recoveries were not more numerous after transfusion than without it, and remarks that failure to find any means of keeping the fluid in the vessels caused the plan to just miss being "a great and glorious discovery." In 1906, with the assistance of Captain J. W. D. Megaw, I. M. S., I tried large intravenous injections of normal saline, controlled by the blood-pressure, in the belief that sufficient quantities had

not been formerly used. The results, however, were very disappointing, the diarrhea usually being rapidly restarted, collapse often returning within about three hours. A few lives appeared to be saved, but no very material effect was produced on the year's death-rate from the disease.

THE INDICATIONS FOR THE USE OF HYPER-
TONIC SALINES IN CHOLERA.

On further consideration it seemed probable that with the concentration of the blood in cholera the percentage of salts in the blood became raised, and that this was a conservative process tending to check the further loss of fluid by causing it to run into rather than out of the blood, and so check the diarrhea. By diluting the salts in the blood once more by injecting normal saline solution the outflow of fluid from the blood would be restarted. If this were the case the indication would be to inject hypertonic solutions, so as to replace the lost fluid and at the same time maintain the protective high percentage of salts. In 1908 I had an opportunity, in conjunction with Captain Maxwell Mackenzie, I. M. S., to test this measure, with the result of an immediate reduction of the mortality of cholera at the Calcutta Medical College Hospital by nearly one-half. At the same time I made a series of estimations of the chlorides in the blood, both before and after

the hypertonic injections, with most instructive results. Thus, I found that in the most severe cases of cholera the chlorides are not only not increased in amount, but may be actually reduced below the normal. In Bengal the salts in the blood are higher than in Europeans, Captain McCay, I. M. S., having found them to be about 1 per cent, and the chlorides 0.8 per cent or over. In many bad cholera cases the chlorides frequently are only between 0.6 and 0.7 per cent, while in some such cases the blood was either absolutely incoagulable or the serum after clotting showed actual hemolysis.

Immediately after hypertonic injections neither of these changed conditions remained, while if the chlorides were raised to 1 per cent or over collapse rarely recurred; but if they were still only 0.8 to 0.9 per cent after the injections relapses often occurred. In milder cases, on the other hand, the chlorides may be normal or slightly increased, from 0.8 to 1 per cent having been frequently found. There is thus a relationship between the loss of chlorides from the blood and the death-rate, and a strong scientific basis for the use of hypertonic saline injections in cholera is established by these observations. As pointed out by Edmund Parkes as long ago as 1849, cholera rice-water stools contain from 0.5

to 1 per cent of chlorides, an observation which I have repeatedly confirmed. Thus the salts are also lost from the blood and require to be replaced as well as the fluids.

Strength of Salt Solution Used.—During 1908 I used a solution containing 120 grains of sodium chloride to a pint of water, or 1.35 per cent, having a specific gravity of 1006 at 70° F. During the first half of 1909 I increased it to 150 grains of sodium chloride and 3 grains of calcium chloride to one pint, with no change in the death-rate. In view of the fact that I am now using still larger quantities injected more slowly, as described further on, I now prefer the former strength of two drachms to the pint, with 3 grains of calcium chloride per pint in the first three or four pints only, on account of the low coagulability of the blood in severe cholera. In view of the favorable results obtained with these solutions I have not attempted to complicate matters by the addition of other salts normally present in the blood. The same strength is used for rectal injections during the collapse stage, but normal saline is preferable in the later stages after reaction, when its use is continued until the kidneys act freely. When salines are given subcutaneously or intraperitoneally the hypertonic solution is used and is readily absorbed.

RESULTS OBTAINED WITH HYPERTONIC
SALINE INJECTIONS IN CHOLERA.

Calcutta is an ideal place for studying cholera, as a month never passes without the occurrence of cases, although they are much more numerous in the first half of the year, and the mortality is somewhat higher during the first quarter. Records of the mortality are available for a number of years, that of 417 cases in the six years from 1902-1905, before transfusions were commonly carried out, having been 61.2 per cent, the figure not varying widely in different years. The hypertonic solutions were commenced in the middle of January, 1908, and during the year 176 cases were treated with a mortality of only 33.5 per cent, including moribund and complicated cases.

Season of 1909.—As the great majority of the cholera cases in Calcutta occur during the first half of the year the results from January to early in August (the time of writing) comprise the whole of the regular cholera season and may be recorded here, as they have not yet been published. Omitting seven cases which occurred during my absence from Calcutta, and were not fully treated by my method, there have been 102 cases with a mortality of 34.3 per cent, a figure almost identical with that of the previous year. Combining the two years

we have a death-rate among 278 cases of 33.8 per cent, or but little more than one-half of the rate when transfusion was very rarely used at the Medical College Hospital. Again, during 1908, 110 cases were actually treated by intravenous hypertonic transfusions with a death-rate of only 41.8 per cent, against 84 per cent in Latta and Mackintosh's series and over 70 per cent in Wall's cases—very strong evidence as to the advantages of the hypertonic solutions over the normal saline which they used, and greatly to the credit of Captain Mackelvie, who carried out the injections during that year.

Causes of Death in the 1909 Series.—The stage and mode of death in the fatal cases is shown in the following table. The figures are worthy of study as indicating the lines of further possible advance in reducing the mortality of the disease:

TABLE OF CAUSES OF DEATH IN 102 CASES OF CHOLERA.

	Deaths.	Percentage of total cases.
Collapse	14	13.7
Reaction stage, including hyperpyrexia	9	8.8
Uremic stage	7	6.9
Pneumonia and bronchitis.....	5	4.9

Collapse.—The fact that only 14 per cent of the total cases treated, including one dying a few minutes after admission, were lost in the collapse stage affords very clear evidence of the great value of the hypertonic transfusions. At the same time it shows

that a few very severe cases will be lost from collapse in spite of it, although among the last 58 cases treated in my ward, under new arrangements permitting of an assistant surgeon being available for transfusing cholera patients both day and night, only 10 per cent of deaths from collapse have occurred. Nevertheless, fatal collapse may occur in very severe cases some hours after, as much as four pints having been injected into the veins, as in one patient who passed three pints of rice-water stool at once and died before transfusion could be repeated. The difficulty in dealing with such cases is that four pints run in fairly quickly, say in half an hour, but raise the blood-pressure to the normal limit and dilute the blood below the normal, so that larger quantities cannot well be given in this way. In order to get over this difficulty I have had a stop-cock transfusion cannula made by Down Bros. of London, by means of which, after running in three or four pints rapidly, the current can be slowed to any desired extent (as described above), and slow injection can be continued for some hours, as it will pass into the tissues without further diluting the blood or raising the pressure to a dangerous extent. Further experience is required to allow of the exact value of this method being gauged, but so far it promises well.

Stage of Reaction.—Nearly all the older

writers describe the period of reaction, with recovery of the pulse after the collapse stage is over, as a very dangerous time in cholera. During the present year 9 per cent of the total cases died in this stage, or not very much less than in the collapse period. The main feature of such cases is usually a marked rise of temperature, which either continues high, a typhoid-like state ensuing, or in very severe cases hyperpyrexia has been considerably lowered, with an early fatal result. These conditions appear to be due to absorption of toxins from the intestinal canal following the restoration of the blood-pressure, and are extremely difficult to combat. During the present year hyperpyrexial cases have been unusually prevalent and fatal both in the Medical College and the European Hospital, thus constituting a special and very severe type of the disease, three out of the eight deaths in the reaction stage having been due to this condition, which may come on shortly after transfusion, or not until some hours later. The cold bath appears to be the only measure likely to control the temperature, but heart failure may ensue, and this of itself is an occasional cause of death in feeble subjects during reaction without any marked rise in temperature. I should mention that a slight rigor, with a temporary rise of temperature up to 103° F., is very common after transfusion, but is not an unfavorable

symptom, being usually accompanied by a good blood-pressure. An increase in the respiratory rate is commonly a sign of a severe reaction, and an indication for ammonia stimulants, such as ammonium carbonate and sal volatile, while if cyanosis ensues oxygen inhalations appear to be indicated. Alcohol should be avoided as far as possible as it tends to increase the vasomotor paralysis.

Lung Complications.—Wall records that pneumonia and other lung complications are more prevalent in temperate than in tropical climates after cholera. During this year they have been unusually frequent in Calcutta, 5 per cent of the deaths being due to them, including one case of acute bronchitis on the ninth day of convalescence. These complications proved fatal from the fourth to the ninth day after admission. They nearly all occurred in a badly ventilated basement, only one case having been seen since a new airy ward has been in use. Ammoniacal preparations have here also been of most use.

DEFICIENT BLOOD-PRESSURE AS THE CAUSE OF POST-CHOLERAIC UREMIA.

By far the most important and fatal complication during the later stages of cholera has hitherto been the failure of the kidneys to resume their excretory functions after the long stasis of the renal circulation dur-

ing the collapse stage. Little or no urine is excreted, and after a few days death ensues from a combination of uremia and retention of cholera toxins.

In 1907, when intravenous injections were rarely given, the death-rate in the uremic stage was 13.2 per cent of the admissions. The extended use of the hypertonic transfusions during 1908 might have been expected to increase this proportion by tiding so many severe cases over the collapse stage, to face the dangers of uremia; just as post-diphtheric paralysis is more frequent after the use of the serum treatment in cases which would otherwise have died at an earlier stage. The figure for the latter year, however, was almost the same, namely 12.8 per cent, and a considerable number of these deaths were in patients admitted late after reaction, and who had not been transfused. This favorable result is doubtless due to the transfusions greatly lessening the duration of renal stasis during collapse and being often quickly followed by the free passage of urine. I further found, as already recorded elsewhere, that uremic symptoms only ensued when the blood-pressure remained for some days below 100 mm.; while by perfusing saline solutions through the renal circulation post mortem I discovered that a pressure of from 90 to 100 millimeters of mercury was required to get a good stream back through

the renal veins of kidneys from patients dying of choleraic uremia, against one of 20 to 30 mm. in the kidneys of ordinary diseases. It was thus shown that the suppression of urine after cholera is really due to the failure of restoration of the circulation through the kidneys, which have become intensely congested and full of hemorrhages during the collapse stage.

The obvious indication is to endeavor to force up the blood-pressure to well over 100 mm., steps being taken as soon as reaction occurs, two or three days being then available as a rule before very urgent symptoms will ensue. During the present year I have taken the blood-pressure daily in all cases with the mercury manometer (Riva-Rocci's instrument), with the result of demonstrating that every patient whose blood-pressure remained for several days below 100 mm. died with uremic symptoms, while only one case with a pressure of 105 mm. or over thus died, and in this instance early granular change in the kidneys was found post mortem.

The measures used to raise the blood-pressure when deficient in the later stages were the following: In the first place half to one pint of normal saline solution is given per rectum every two to four hours, 5 minims of a 1-in-1000 solution of adrenalin chloride being added to each first; secondly, dry cupping over the kidneys is carried out

morning and evening to relieve congestion; thirdly, digitalin grain 1/100 is given subcutaneously twice a day, and if this fails strophanthin, up to 1/100 of a grain, is administered intravenously, and was apparently successful in two cases. The result of this line of treatment has been to reduce the death-rate from uremic symptoms during the present year to 6.9 per cent, or barely half of that of the previous two years, and this serious complication is now much less dreaded than formerly.

Opium or morphine after collapse has once set in predisposes to uremia later. I tried giving it to check the diarrhea after restoring the blood-pressure by transfusion, but abandoned it, as uremia was distinctly more frequent after its use.

THE LIMITATIONS OF THE VALUE OF HYPERTONIC TRANSFUSION IN CHOLERA.

The reduction in the death-rate from cholera by nearly one-half the former rate at the Calcutta Medical College Hospital during two consecutive years among nearly three hundred cases, affords strong evidence of the value of the hypertonic saline transfusions controlled by the blood-pressure records, based as the method is on the blood changes I have described. It must, however, be clearly borne in mind that after all only the symptoms and results of the disease are being combated, while the cause is not

touched, so that it fails in exceptionally virulent infections with excessive production of toxins in the small bowel, as in the terrible hyperpyrexial form of the disease. Moreover, cholera is usually of the sporadic form among natives in Calcutta, and consequently more amenable to treatment than sudden very virulent epidemic cases, in which equally good results are not to be expected, although the principles of treatment remain unchanged for them. Even here it is possible in the great majority of cases to prevent death in the collapse stage, and thus afford many hours' time for the use of remedies directed toward the destruction of the infective agent and its toxins in the intestinal canal. It is in this direction that further progress is now being sought for, and I am sanguine enough to believe that a still further reduction of the mortality will before long be obtained on these lines.



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